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# Synthesis of Sulfoximine-Derived P,N Ligands and their Applications in Asymmetric Quinoline Hydrogenations

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Dedicated to Prof. Dr. Andreas Pfaltz on occasion of his 60th birthday.

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**Abstract:** A series of naphthalene-bridged P,N-type sulfoximine ligands and their iridium complexes have been synthesized. They were applied in the enantioselective hydrogenation of quinoline derivatives, and enantioselectivities up to 92% *ee* have been achieved in the hydrogenation of 2-methylquinoline.

**Keywords:** asymmetric catalysis; enantioselectivity; hydrogenation; iridium; quinolines; sulfoximines

## Introduction

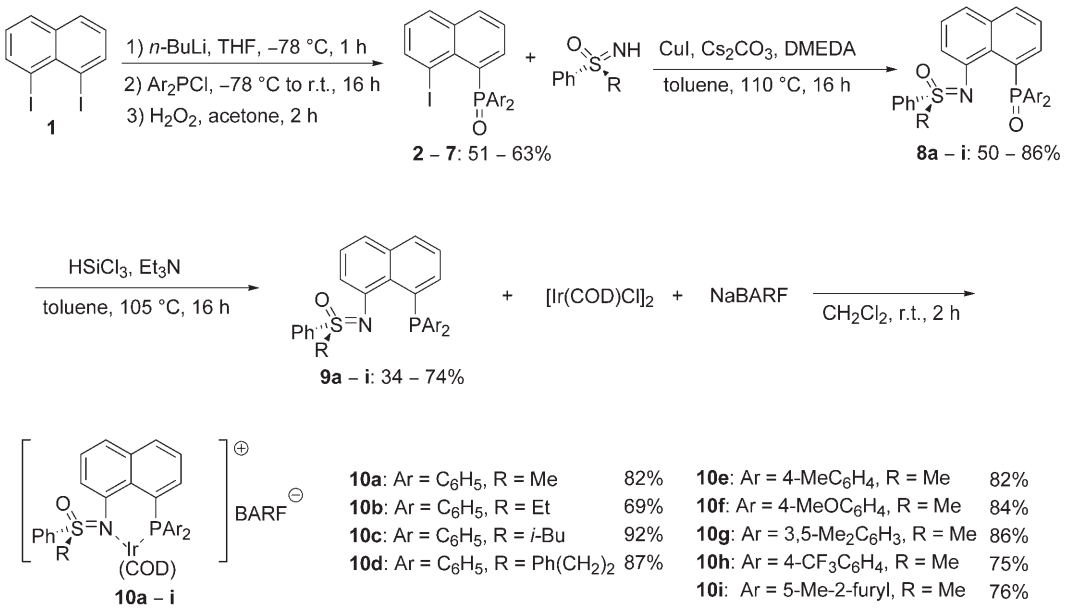
Ligands which bear phosphorus and nitrogen as the donor atoms are among the most important and widely used heterodentate ligands in asymmetric metal catalysis.[1] Best known are phosphinooxazolines, which proved highly useful for various enantioselective transformations including allylic substitutions, conjugate enone additions and olefin hydrogenations.[2] Sulfoximine-based compounds of this type are rare. This is surprising considering that related N,N- and N,O-type sulfoximines proved widely applicable as chiral ligands in a number of asymmetric catalyses leading to products with high enantiomeric excesses. Examples include (hetero)-Diels–Alder, Mukaiyama-type aldol and carbonyl-ene reactions as well as additions of diorganozinc reagents to carbonyl and heterocarbonyl compounds.[3,4] Just recently benzene-bridged P,N ligands with sulfoximidoyl substituents were synthesized and their application in asymmetric hydrogenations of acyclic ketimines yielded amines with up to 98% *ee*.[5] Encouraged by these results, we decided to synthesize naphthalene-bridged P,N-type sulfoximines[6] and to test their efficacy as ligands in asymmetric hydrogenation reactions.

## Results and Discussion

Following methodology developed earlier in our group,[6,7] treatment of 1,8-diiodonaphthalene (**1**, prepared from 1,8-diaminonaphthalene[8]) with *n*-BuLi (−78 °C, 1 h) followed by addition of $ClPAr_2$ (−78 °C, 30 min, then 25 °C, 16 h) led to diarylphosphine derivatives, which could be oxidized by $H_2O_2$ (25 °C, 2 h) affording phosphinoylnaphthalenes **2–7** in moderate yield (51–63% over two steps). No aqueous work-up was required after the phosphorylation, and it was possible to simply evaporate the solvent after the first step and change to acetone in the second. Then, using a copper-catalyzed cross-coupling reaction,[9] compounds **8a–i** were obtained in yields ranging from 50 to 86%. Subsequent reductions of the phosphine oxides using $HSiCl_3/Et_3N$ afforded naphthalene-bridged phosphanylsulfoximines **9a–i** in 34–74% yield (Scheme 1). Unfortunately, the commonly used method for the preparation of iridium complexes {mixing of the P,N ligand with $[Ir(COD)Cl)]_2$ in dichloromethane followed by the addition of NaBARF and water}[10] proved sluggish, giving inseparable mixtures of the desired complexes and impurities (according to $^{31}P$ NMR). Following Zhou's protocol,[11] however, complexes **10a–i** were accessible in high yields (69–92%; Scheme 1).

With the goal to investigate the effect of the alkyl substituent at the sulfoximine moiety on the catalytic activity, complexes **10a–d** were synthesized. Based on the results of the hydrogenation of 2-methylquinoline (**11a**), complexes **10e–i** bearing various aryl substituents at the phosphorus atom were prepared. All of these complexes were stable to oxygen and moisture allowing purifications by flash column chromatogra-

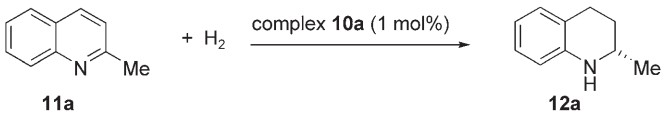



**Scheme 1.** Syntheses of sulfoximine-based P,N ligands and their iridium complexes.

phy on silica gel and handling in the laboratory atmosphere.

Next, asymmetric hydrogenations of quinolines were investigated using complexes **10a–i** as catalysts.[12] The first reaction was carried out with 1 mol% of complex **10a** in $CH_2Cl_2$ at room temperature under 40 bar of $H_2$ pressure using 2-methylquinoline (**11a**) as the model substrate. Disappointingly, only a trace of product could be detected by $^1$H NMR after 20 h (Table 1, entry 1). However, when toluene was used as the solvent under the same conditions, 45% conversion of **11a** was achieved and **12a** was formed with 88% *ee* (entry 2). After increasing the hydrogen pressure to 60 bar, the reaction temperature and time were optimized, and the results of those studies are listed in Table 1 (entries 3–7).

**Table 1.** Asymmetric hydrogenation of 2-methylquinoline (**11a**) to give **12a** under various conditions with complex **10a**.[a]




| Entry | Solvent | $H_2$ [bar] | Temp. [°C] | Time | Conv. [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | 40 | r.t. | 20 h | <5 | - |
| 2 | toluene | 40 | r.t. | 20 h | 45 | 88 |
| 3 | toluene | 60 | r.t. | 3 d | 92 | 92 |
| 4 | toluene | 60 | r.t. | 6 d | >95 | 90 |
| 5 | toluene | 60 | 40 | 2 d | 90 | 90 |
| 6 | toluene | 60 | 50 | 20 h | 88 | 90 |
| 7 | toluene | 60 | 60 | 20 h | >95 | 87 |

[a] *Reactions conditions:* **11a** (0.5 mmol), catalyst **10a** (1 mol%), solvent (1.5 mL). All the reactions were carried out under argon.

[b] Conversions were determined by $^1$H NMR.

[c] Enantiomer ratios were determined by HPLC using a Chiralcel OD-H column. The *S* enantiomer of **12a** was formed in excess.

Extending the reaction time at room temperature to 3 days led to an improved conversion of **11a** (92%) and an enantioselectivity of 92% *ee* for **12a** (Table 1, entry 3). Prolonging the reaction time to 6 days gave full conversion but a product with slightly lower *ee* (90%; entry 4). If the reaction was carried out at 40 or 50 °C and for a shorter time, a trace of substrate remained (entries 5 and 6). Finally at 60 °C after 20 h, complete conversion and good enantioselectivity (87% *ee*) were achieved (entry 7).

In order to improve the asymmetric quinoline hydrogenation further, the effects of additives[13] were investigated under the optimal conditions. Iodine, which is a commonly used additive and essential in other hydrogenations of quinolines,[12] had a negative effect, leading to incomplete conversion and very low *ee* (Table 2, entry 1). Other compounds such as NIS and NBS gave >90% conversions of **11a**, but the *ee* of **12a** was <10% (entries 2 and 3). Surprisingly, the absolute configuration of the product was reversed in the presence of $I_2$ and NIS. When $Bu_4NBr$ and $Bu_4NI$ were added to the reaction mixture, no product was detected (entries 5 and 6). The same result was observed (with or without iodine) in attempts to produce an efficient *in situ* catalyst {by combining the P,N ligand and $[Ir(COD)Cl)]_2$ before the reaction start}.

**Table 2.** Effect of additive on the hydrogenation of 2-methylquinoline (**11a**) to give **12a** (see Table 1 for Scheme).[a]

| Entry | Additive | Conv. [%][b] | *ee* [%][c] | Entry | Additive | Conv. [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|---|---|
| 1 | $I_2$ | 93 | −8 | 4 | KI | >95 | 77 |
| 2 | NIS | >95 | −8 | 5 | $Bu_4NBr$ | <5 | - |
| 3 | NBS | 92 | 5 | 6 | $Bu_4NI$ | <5 | - |

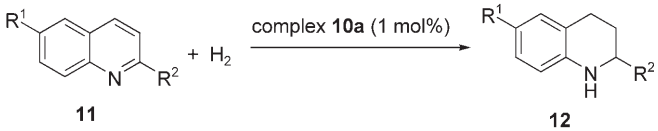
[a]–[c] As in Table 1; at 60 °C, 20 h reaction time . A negative sign under *ee* indicates the reversed absolute configuration of the product.

Next, complexes **10b–i** were evaluated in the hydrogenation of 2-methylquinoline (**11a**) under the optimized conditions (Table 3).

Increasing the steric bulk of the alkyl substituent of the sulfoximidoyl moiety lowered the enantioselectivity of the resulting catalyst. Thus, using **10b**, **10c** and **10d** bearing an ethyl, isobutyl or a phenethyl group at the sulfur atom resulted in the formation of **12a** with only 76, 41 and 35% *ee*, respectively (Table 3, entries 1–3; compared to 87% *ee* achieved with methyl-substituted **10a**). Substitutions of the phenyl group at the phosphorus atom had no obvious effect on the performance of the resulting catalysts. Thus, similar conversions (93–>95%) and enantioselectivities (64–78% *ee*) were obtained with complexes bearing either electron-donating (MeO-, Me-, 3,5-diMe) or electron-withdrawing ($CF_3$-) groups (Table 3, entries 4–7). A significant deviation in conversion and *ee* was observed in the reaction with complex **10i** having a 5-methyl-2-furyl substituted P,N ligand. There, the conversion of **11a** was only 84% and **12a** had 23% *ee*. $^{31}P$ NMR studies confirmed the difference between complexes **10e–h** and **10i**. Whereas the former showed very similar chemical shifts (around 17.5–19.7 ppm), the latter had a $^{31}P$ NMR chemical shift of −10.2 ppm, indicating that this phosphorus atom was much more electron-rich.

To assess the substrate scope, a variety of substituted quinoline derivatives were hydrogenated under the optimized conditions using complex **10a** as catalyst. As shown in Table 4, both reactivity and enantioselectivity depended on the substitution pattern of the substrate. When the substituent at the 2-position of the quinoline was changed from methyl to ethyl, *n*-propyl, isobutyl or *n*-pentyl groups, both conversion and enantioselectivity decreased (entries 2–7). Even after a prolonged reaction time of 48 h, the quinoline conversions remained incomplete and, surprisingly, the enantioselectivites were lower (entries 3 and 5). For the 2,6-disubstituted quinolines the reaction proceeded well, when the substituents at the 6-position were electron-donating groups such as Me or MeO (full conversions of **11f** and **11h** after 24 h; entries 8 and 10). In contrast, the hydrogenation reaction was

**Table 4.** Hydrogenation of quinoline derivatives **11** using complex **10a**.[a]




**11** **12**

| Entry | $R^1$ | $R^2$ | Compd. | Time [h] | Conv. [%] | *ee* [%][c] Abs. Conf.[d] |
|---|---|---|---|---|---|---|
| 1 | H | Me | **11a** | 20 | >95 | 87 (*S*) |
| 2 | H | Et | **11b** | 24 | 62 | 77 (*S*) |
| 3 | H | Et | **11b** | 48 | 69 | 70 (*S*) |
| 4 | H | *i*-Bu | **11c** | 24 | 53 | 75 (*R*) |
| 5 | H | *i*-Bu | **11c** | 48 | 71 | 55 (*R*) |
| 6 | H | Pr | **11d** | 24 | 62 | 80 (*S*) |
| 7 | H | Pent | **11e** | 48 | 90 | 65 (*S*) |
| 8 | Me | Me | **11f** | 24 | >95 | 75 (*S*) |
| 9 | F | Me | **11g** | 24 | 43 | 64 (*S*) |
| 10 | MeO | Me | **11h** | 24 | >95 | 78 (*S*) |

[a] *Reaction conditions:* **11** (0.5 mmol), catalyst **10a** (1 mol%), toluene (1.5 mL), 60 °C. All the reactions were carried out under argon.
[b] As in Table 1
[c] As in Table 1.
[d] Determined by comparison of rotation sign with the literature data[14a] or assuming analogous reaction pathways (for entries 4 and 5).

**Table 3.** Hydrogenation of 2-methylquinoline (**11a**) to give **12a** using complexes **10b–i** (see Table 1 for Scheme).[a]

| Entry | Complex | Conv. [%][b] | *ee* [%][c] | Entry | Complex | Conv. [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|---|---|
| 1 | **10b** | 95 | 76 | 5 | **10f** | 94 | 76 |
| 2 | **10c** | 61 | 41 | 6 | **10g** | 96 | 66 |
| 3 | **10d** | 91 | 35 | 7 | **10h** | >95 | 64 |
| 4 | **10e** | 93 | 78 | 8 | **10i** | 84 | 23 |

[a]–[c] As in Table 1; at 60 °C, 20 h reaction time.

slow with substrate **11g** having an electron-withdrawing group at C-6 (Table 4, entry 9).

## Conclusions

We have described the synthesis of naphthalene-bridged P,N-type sulfoximine ligands and demonstrated their catalytic potential in the enantioselective iridium-catalyzed hydrogenation of quinolines. Further applications of this class of ligands in asymmetric catalysis are under investigation.

## Experimental Section

The detailed characterization data of compounds **2–7**, **8a–i**, **9a–i**, **10a–i** and the HPLC conditions for compounds **12a–h** are given in the supporting information.

### General Procedure for the Preparation of Compounds 2–7

To a solution of 1,8-diiodonaphthalene (**1**, 1.9 g, 5.0 mmol) in anhydrous THF (20 mL) was added *n*-BuLi (3.2 mL, 1.6 M in hexane, 5.0 mmol) at −78 °C under an argon atmosphere. The mixture was stirred at −78 °C for 1 h, and then $Ar_2PCl$ (5.0 mmol) was added dropwise. After stirring for 30 min, the cooling bath was removed, and the reaction mixture was stirred overnight at room temperature. Then, the solvent was removed under vacuum. To the residue dissolved in acetone (10 mL) was added an excess amount of $H_2O_2$ (30%, 2.0 equiv.) in an ice bath. After stirring at room temperature for 2 h, the solvent was removed and the residue was directly purified by flash chromatography (silica gel, pentane/EtOAc, 1:1–1:5 as the eluent) yielding the target compound as a solid.

### General Procedure for the Preparation of Compounds 8a-i

Under an argon atmosphere, a 50-mL of Schlenk-flask was charged with the (*S*)-sulfoximine (5.5 mmol), **2–7** (5.0 mmol), CuI (0.5 mmol), and $Cs_2CO_3$ (12.5 mmol). The mixtures were dissolved in distilled toluene (20 mL). Then DMEDA (1.0 mmol) was added. After being heated to 110 °C overnight, the mixture was cooled to room temperature and neutralized with an aqueous solution of HCl (2 M). The aqueous layer was extracted with $CH_2Cl_2$ (3 × 20 mL) and the combined organic extracts were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, pentane/EtOAc, 1:1–1:5).

### General Procedure for the Preparation of Compounds 9a-i

Under an argon atmosphere, a 100-mL dry Schlenk-tube was charged with **8a–i** (1.0 mmol) and distilled toluene (12–20 mL). Then $NEt_3$ (0.8 g, 1.1 mL, 8 mmol) and $Cl_3SiH$ (0.8 g, 0.6 mL, 6 mmol) were added. After stirring at 105 °C for 16 h, the reaction mixture was cooled to room temperature under argon and degassed water (30 mL) was added. Then, the mixture was filtered through celite and washed three times with $CH_2Cl_2$. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 20 mL) and the combined organic extracts were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The product was then purified by flash chromatography (silica gel, pentane/EtOAc, 10:1–3:1).

### General Procedure for the Preparation of Complexes 10a–i

Under an argon atmosphere, a dry Schlenk-tube was charged with (*S*)-*N*-[8-(diphenyl-phosphanyl)naphthyl]-*S*-methyl-*S*-phenylsulfoximine (47 mg, 0.1 mmol), $[Ir(COD)Cl]_2$ (34 mg, 0.05 mmol), NaBARF (133 mg, 0.15 mmol) and dry $CH_2Cl_2$ (3 mL). After stirring at room temperature for 2 h, the product was purified by flash chromatography (silica gel, pentane/$CH_2Cl_2$, 1:1–1:2) to afford the complexes as orange-yellow foaming solids.

### General Procedure for Hydrogenation

A mixture of complex **10a** (8.1 mg, 0.005 mmol) and quinolines **11** (0.5 mmol) was placed in a 5-mL vial equiped with a stirrer bar. Then this vial was put into an argon-filled steel autoclave. To the mixture was added toluene (1.5 mL) under an argon atmosphere. Finally the autoclave was closed and purged three times with hydrogen (less than the pressure needed) and finally pressurized to 60 bar. The reaction mixture was stirred for the indicated period of time. Then, the hydrogen gas was released slowly. The conversion of the reaction was determined by $^1$H NMR spectroscopy of the crude reaction mixture, and the product was purified by chromatography with pentane/EtOAc (10:1). Enantiomer ratios were analyzed with HPLC using a Chiralcel OD-H column. All the products were known compounds. The spectra data of $^1$H NMR and $^{13}$C NMR were accordance with the literature reports.[14]

## Acknowledgements

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